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SMELL IDENTIFICATION FUNCTION IN EARLY ONSET ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT

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Abstract

Little is known about olfactory identification (OI) function in Early Onset Alzheimer's disease (EOAD) and early onset Mild Cognitive Impairment (eoMCI) with age of onset <65 years. We aimed to study OI in EOAD compared to eoMCI and age-matched healthy controls (HC). 19 EOAD subjects with mild to moderate dementia, 17 with eoMCI and 21 HC recruited as convenience sample from memory services were assessed for cognition, behavioral symptoms and activities for daily living. The OI was tested using University of Pennsylvania smell identification test (UPSIT). EOAD participants performed worse compared to eoMCI and HC's on cognitive tests and OI ($p < 0.001$). Although eoMCI had poorer cognitive scores compared to HC, they were similar in their OI function. OI correlated with attention ($r = 0.494$, $p = 0.031$), executive functions ($r = 0.508$, $p = 0.026$) and praxis ($r = 0.455$, $p = 0.05$) within EOAD group. OI impairment was significantly associated with the diagnosis of EOAD versus eoMCI, but not with eoMCI when compared with HC. OI could potentially be useful in differentiating EOAD from eoMCI. Studies with late-life MCI patients showing OI impairment relative to HC may be attributed to a different disease process. Independent replication in larger sample is needed to validate these findings.

Key words: Alzheimer's disease, early onset dementia, smell identification, olfaction, mild cognitive impairment

INTRODUCTION

Olfactory dysfunction in general and impaired olfactory identification (OI) in particular have been reported in Alzheimer's disease (AD) and are found to occur at early stages of the disease (Mesholam *et al.*, 1998). It has been indicated that involvement of the olfactory bulb and tract is one of the earliest events in the degenerative process on the central nervous system in AD (Christen-Zaech *et al.*, 2003) and also that tau pathology in the olfactory bulb increases with severity of AD (Attems *et al.*, 2005). All published reports of OI in AD have demonstrated deficits related to healthy controls (Rahayel *et al.*, 2012) and its utility as a biomarker to predict cognitive decline and AD in elderly cognitively normal people and those with mild cognitive impairment (MCI) (Devanand *et al.*, 2015; Lafaille-Magnan *et al.*, 2017; Woodward *et al.*, 2017). A recent meta-analysis has shown that OI amongst the olfactory deficits to be most impaired in MCI (average age 72.83 years) (Roalf *et al.*, 2017). Strong correlations of OI with cognition in AD patients have been identified, showing the potential of OI testing as a disease and progression marker (Suzuki *et al.*, 2004; Velayudhan *et al.*, 2013).

Early-onset dementia is defined as dementia starting before the age of 65, a cut off based on a social partition of retirement age rather than biological one (Rossor *et al.*, 2010).

Although it is well established that patients with late onset AD and elderly MCI perform significantly more poorly than matched controls in their olfactory identification function, there is little information on OI in people with early onset AD (EOAD) and early onset MCI (eoMCI) (<65 years) compared to control subjects. We aimed to establish differences in OI

function between people with EOAD, eoMCI and age-matched healthy controls (HC), and to study the association of OI function with cognition and non-cognitive symptoms.

METHODS

Subjects:

Mild-moderate EOAD participants (Mini Mental State Examination score, MMSE; 15-25) (n=19) were recruited from Young Onset Dementia Assessment Service (YODAS) within Mental Health Services for Older People (MHSOP), Leicestershire Partnership National Health Service (NHS) Trust, UK. They had onset of symptoms and diagnosis of dementia < 65 years of age. Diagnosis of probable AD was made according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann *et al.*, 1984). The exclusion criteria were dementia other than AD; history of psychiatric disorder, including substance abuse.

eoMCI Participants (MMSE score 24-30) (n=17) aged < 65 years, were recruited following clinical diagnosis as per ICD 10 code (F06.7) from YODAS within MHSOP, Leicestershire Partnership NHS Trust, UK. Diagnosis of MCI was made following a semi structured interview with an experienced psychiatrist, comprehensive cognitive testing and dementia screen, including blood testing and neuroimaging. Exclusion Criteria included history of any type of dementia or psychiatric disorder.

Healthy Controls (HC) (n=21) were recruited from a group of interested healthy volunteers (9 domestic partners, 4 first degree relatives and 8 unrelated volunteers) and were within +/- 5 years of age of the EOAD and eoMCI participants. They had no complaints of memory

or functional decline. They did not have diagnosis of dementia or MCI. The MMSE score range was 27-30.

The exclusion criteria were those with diagnosis of dementia, significant neurological or psychiatric illness, significant unstable systematic illness or organ failure.

All participants had either no history at all of cigarette smoking or had stopped smoking for 20 years or more. They also did not have acute or chronic medical conditions that may affect cerebral functioning or other conditions known to affect olfactory functioning such as common cold, polyps.

Informed consent or assent, as appropriate was taken from all the participants. The study had approval from East Midlands region NHS Research Ethics Committee and the recruitment was completed during the period 2013-2015.

Assessments

Assessment included cognitive testing with MMSE (Folstein *et al.*, 1975) for all 3 groups and CAMCOG part of Cambridge Mental Disorders of the Elderly Examination (CAMDEX) (Roth *et al.*, 1986) in addition for EOAD and eoMCI group. For non-cognitive symptoms Neuropsychiatric Inventory (NPI) (Cummings *et al.*, 1994) and Bristol Activities of Daily Living Scale (BADL) (Bucks *et al.*, 1996) were used. University of Pennsylvania smell identification test (UPSIT) was used, a standardised test for OI (higher scores reflecting better performance) and for which prior evaluation has indicated high reliability (Doty *et al.*, 1984).

Data analysis was done using SPSS 22.0. Comparisons were made on demographic information, clinical characteristics, and cognitive and behavioural test results using the Chi-

square test for categorical outcomes and student t-tests and Spearman rank correlations for continuous variables as appropriate. Logistic regression analysis was carried out with diagnosis (EOAD vs eoMCI and eoMCI vs HC) as the dependent variables and age, sex, education UPSIT, MMSE, CAMCOG and BADL as independent variables.

RESULTS

None of the patient participants had speech or language difficulties. All participants were White Europeans except for 3 EOAD patients (Asian), 5 eoMCI patients (1 Afro-Caribbean and 4 Asian) and 1 HC (Asian).

The socio-demographic and clinical comparisons between the subjects with EOAD, eoMCI and the HC are as described in Table 1. The EOAD group scored lower on the MMSE ($t(34) = -2.980$, $p = 0.005$) and UPSIT measures ($t(34) = -4.153$, $p < 0.001$) than eoMCI and similarly scored lower on MMSE ($t(38) = -5.389$, $p < 0.001$) and UPSIT ($t(38) = -3.448$, $p = 0.001$) compared to HC. The eoMCI participants scored lower than HC group on the MMSE ($t(36) = -4.241$, $p < 0.001$); however, there was no difference between the two groups on UPSIT scores ($t(36) = 0.188$, $p = 0.852$). Total UPSIT scores correlated with MMSE ($r = 0.462$, $p < 0.001$) and total CAMCOG ($r = 0.509$, $p < 0.001$) for the EOAD and eoMCI groups. Within the EOAD group the total UPSIT scores correlated with MMSE ($r = 0.477$ and $p = 0.039$) and with CAMCOG subitems i.e., executive functions ($r = 0.508$, $p = 0.026$), attention ($r = 0.494$, $p = 0.031$) and praxis ($r = 0.455$, $p = 0.050$).

Logistic regression analysis using both adjusted and unadjusted models showed that UPSIT was the only variable that significantly predicted the diagnosis of EOAD versus eoMCI (odds

ratio 1.25; 95% CI 1.006, 1.558; $p=0.04$), over the cognitive measures (table 2A). Whereas MMSE predicted diagnosis of eoMCI versus HC.

There were no sex differences in the UPSIT scores for the whole sample and individual groups. The UPSIT scores did not correlate with total NPI or total BADL for the EOAD group.

DISCUSSION

The study investigated OI deficits in early onset AD and MCI, an area where there is lack of data and is understudied. Albeit in a small sample, the findings of our study are interesting in that it shows impaired OI in people with EOAD compared to eoMCI and HC. Impairment in OI was significantly associated with EOAD diagnosis versus eoMCI, adjusting for age, sex, education, MMSE and CAMCOG. As previously identified in late onset AD (Velayudhan *et al.*, 2013), a strong relationship between olfaction and cognition was also found in EOAD subjects. There was no difference in UPSIT scores between eoMCI and HC subjects, i.e., eoMCI had no OI impairment.

The mean UPSIT scores for our EOAD cohort was higher than seen in later onset AD studies (mean from 18.1 to 20.6) (Rahayel *et al.*, 2012; Velayudhan *et al.*, 2015). We found no sex differences for olfactory identification deficits which is in keeping with previous study (Djordjevic *et al.*, 2008). None of the patient participants reported subjective impairment in olfaction voluntarily. Interestingly, only 6% of late onset AD patients were aware of their olfactory impairment, despite being identified in 90% (Doty *et al.*, 1987). Also its now reported that in cognitively healthy participants, subjective loss of smell is an independent predictor of dementia onset (Stanciu *et al.*, 2014) and mortality (Ekstrom *et al.*, 2017), but in

cognitively compromised patients, smell deficits go unnoticed.

UPSIT scores in eoMCI group in our study did not differ from HC contrary to the reports from previous studies albeit in older adults (Roalf *et al.*, 2017). Without validation of these results, a link between olfaction and eoMCI cannot be ruled out, although presence of a different disease-causing process to that of elderly MCI could be considered. It is also interesting to note that eoMCI patients in our study had higher prevalence of TIA, MI and diabetes which are known risk factors for vascular cognitive impairment (table 1), and possibly our study eoMCI participants are not necessarily pre-AD or developing AD pathology.

We found OI was associated with attention, executive function and praxis within EOAD group. Previous research has found a relationship between olfaction and attention/executive functioning in healthy older adults, MCI, and AD (Djordjevic *et al.*, 2008; Lehrner *et al.*, 2009; Makizako *et al.*, 2014). Impairment in odour identification in mid-life (35–64 years) has been associated with slightly poorer performance on cognitive function tests of attention, processing speed and executive function (Schubert *et al.*, 2013).

Clinically, challenges are seen in AD diagnosis despite comprehensive guidelines (McKhann *et al.*, 2011; WHO, 2015). This is particularly in younger patients where AD is uncommon and less likely to be considered as part of a differential diagnosis, especially in the absence of a suggestive family history. Subsequently, for many patients this can lead to a lengthy, drawn out period between initial symptoms of dementia and ultimate specialist referral and

diagnosis. Although current biomarkers are invaluable in AD diagnosis, many are expensive and particularly invasive procedures rendering them difficult for extensive use in screening for dementia. The need to aid diagnosis ideally through cheap, non-invasive, reliable tools is apparent. OI testing has been suggested as a potential tool for increasing diagnostic accuracy in AD as a clinical biomarker adjunct (Wesson *et al.*, 2010).

The main limitation of the study is the small sample size. The limitations of this study include the cross-sectional design which prohibits determining causality or direction of the associations seen. A further limitation, which could be overcome in future research, is to make additional comparisons with different groups, such as adults of a similar age with cognitive impairment with other neurodegenerative disorders. The strengths of this study include the well-defined participants and the use of standardized measures of odor identification and cognitive function that were administered by trained researchers. In addition, detailed demographic, health and behavioral data were available.

In conclusion, albeit in a small sample, our study found impaired OI in people with EOAD compared to eoMCI and HC and also that OI impairment was significantly associated with a diagnosis of EOAD (versus eoMCI) while cognitive tests were not. OI in EOAD was associated with poorer performance in attention, executive functions and praxis. Further work, with larger cohorts, including people with different causes of cognitive impairment and in longitudinal studies is needed. This will give greater insight into the potential of OI testing used in combination with other diagnostic tests, for improving early detection of EOAD in clinical settings.

Conflict of interest: None

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Author responsibilities: LV designed the study, carried out the data collection, performed statistical analysis and interpretation. TB, SB, AJ, FM and EP contributed to the data collection. LV wrote the paper with contributions from all authors. LV had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1: Socio demographic clinical parameters comparison between people with early onset Alzheimer's disease (EOAD), early onset mild cognitive impairment (eoMCI) and healthy controls (HC)

Variables	EOAD (n=19)	eoMCI (n=17)	HC (n=21)
Mean (SD) or %			
Female	7 (36.8%)	6 (35.3%)	10 (47.6%)
Age (years)	59.39 (5.3)	58.35 (4.1)	60.7 (11.2)
Education (years)	11.59 (3.4) ^b	12.56 (2.7) ^c	15.5 (3) ^{b, c}
Disease Duration (months)	3.5 (4)	3.3 (2)	n/a
Family h/o dementia	8 (42.1%)	7 (41.2%)	11 (52.4%)
MMSE	21.89 (6.3) ^{a, b}	26.82 (2.6) ^{a, c}	29.43 (0.9) ^{b, c}
CAMCOG total	74.47 (16.9) ^a	89.53 (7.8) ^a	n/a
Executive functions	19.53 (4.1) ^a	15.21 (4.9) ^a	n/a
40 UPSIT items	23.05 (6.6) ^{a, b}	31.47 (5.4) ^a	31.05 (7.9) ^b
40 UPSIT, time taken (minutes)	24.13 (8.7) ^{a, b}	16.63 (6.2) ^a	17.88 (4.1) ^b
BADL	8.74 (7.1) ^a	4.00 (4.5) ^a	n/a
NPI	16.0 (17.9)	15.77 (17.1)	n/a
Total carer's distress	10.16 (9.4)	6.24 (7.2)	n/a
h/o diabetes mellitus	2 (10.5%) ^a	7 (41.2%) ^{a, c}	0 ^c
h/o hypertension	4 (21.1%)	7 (41.2%)	7 (33.3%)
h/o TIA	0	2 (11.8 %) ^{a, c}	0
h/o MI	0	2 (11.8 %) ^{a, c}	0

^a EOAD vs eoMCI; ^b EOAD vs HC; ^c eoMCI vs HC (statistically significant between the groups, $p < 0.05$)
Values are mean (SD) or n (%)

AD, Alzheimer's disease; HC, healthy controls; eoMCI, early onset mild cognitive impairment, TIA, transient ischaemic attack; MI, myocardial infarction; MMSE, Mini Mental State Examination; CAMCOG, Cambridge Cognition Examination; UPSIT, University of Pennsylvania Smell Identification Test (higher UPSIT scores reflect better performance); BADL, Bristol Activities of daily living, NPI, Neuropsychiatric Inventory; n/a, not applicable; h/o, history of.

Table 2: Multivariable logistic regression analyses for association of olfactory identification impairment using UPSIT with cognitive diagnosis of early onset Alzheimer's disease (EOAD) versus early onset mild cognitive impairment (eoMCI), and eoMCI versus healthy controls (HC): Model 1- basic model and Model 2- adjusted for age, sex, education and other clinical measures.

	A. EOAD vs. eoMCI		B. eoMCI vs. HC	
	OR (95% CI)	P value	OR (95% CI)	P value
Model 1				
Age	1.136 (0.899 to 1.434)	0.285	1.047 (0.938 to 1.168)	0.415
Sex	1.088 (0.188 to 6.304)	0.925	2.602 (0.358 to 18.924, p= 0.345)	
Education	1.115 (0.808 to 1.539)	0.506	1.461 (1.023 to 2.085)	0.037 *
UPSIT	1.284 (1.069 to 1.544)	0.008 *	0.990 (0.786 to 1.245)	0.928
Model 2				
Age	1.184 (0.878 to 1.596)	0.269	1.070 (0.901 to 1.271)	0.442
Sex	0.901 (0.086 to 9.414)	0.931	1.750 (0.091 to 33.678)	0.711
Education	1.106 (0.733 to 1.670)	0.631	1.109 (0.733 to 1.678)	0.625
UPSIT	1.252 (1.006 to 1.558)	0.044 *	0.827 (0.544 to 1.257)	0.374
MMSE	1.077 (0.595 to 1.949)	0.807	18.113 (1.036 to 316.724)	0.047 *
Total CAMCOG	1.096 (0.864 to 1.391)	0.450	N/A	
Executive functions	1.013 (0.751 to 1.364)	0.934	N/A	
BADL	0.866 (0.672 to 1.116)	0.266	N/A	

Model 1 included diagnosis of EOAD as the dependent variable and age, sex and education as independent variables

Model 2 included diagnosis of EOAD as the dependent variable and sex, age, education, MMSE, total CAMCOG score, executive function scores and BADL as covariates in a multivariable logistic regression model. BADL, executive function and total CAMCOG are not available for model with outcome eoMCI vs. HC.

OR, odds ratio; *, $p < 0.05$; CI, Confidence interval; MMSE, Mini Mental State Examination; CAMCOG, Cambridge Cognition Examination, UPSIT, University of Pennsylvania smell identification test; BADL, Bristol activities of daily living; N/A, Not applicable